

A comparison of analgesic and respiratory effects from tapentadol versus oxycodone after laparoscopic hysterectomy.

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Protocol ID no: Tapentadol study.17031-2.

EudraCT no: 2017-001285-23.

I hereby declare that I will conduct the study in compliance with the Protocol, ICH GCP and the applicable regulatory requirements:

Name	Title	Role	Signature	Date
Marlin Comelon	MD	Principal Investigator		
Kristin Sem Thagaard	MD	Sponsor's representative		

PROTOCOL SYNOPSIS

Title: A comparison of analgesic and respiratory effects from tapentadol versus oxycodone after laparoscopic hysterectomy.

Sponsor: Kristin Sem Thagaard, Oslo University Hospital.

Phase and study type Phase IV, interventional.

Investigational Medical Product (IMP) (including active comparator and placebo): IMP:
Palexia 50 mg® (tapentadol 50 mg)
Palexia depot 50 mg® (tapentadol depot 50 mg)
Active comparator:
OxyNorm 10 mg® (oxycodone immediate-release 10 mg)
OxyContin 10 mg® (oxycodone extended-release 10 mg)

Centers: Oslo University Hospital, Oslo, Norway.

Study Period: Estimated date of first patient enrolled: 01.09.17.
Anticipated recruitment period: 1 year 6 months.
Estimated date of last patient completed: 01.03.19.

Treatment Duration: 24 – 32 hours.

Follow-up: End of treatment visit in person at 24 hours followed-up by a call at 32 hours. No further follow-up visits.

Objectives The primary goal of the study is to examine the analgesic effects in patients receiving either tapentadol or oxycodone during the first postoperative day after hysterectomy.
As a secondary goal we want to examine the respiratory depressive effect from tapentadol compared to oxycodone.

Endpoints: Primary endpoint: Pain at rest 1 hour postoperatively.

Secondary endpoints: Pain at rest and while coughing 1-24 hours postoperatively. Respiratory depression 1-24 hours postoperatively. Further, we will also examine other common opioid related side-effects: sedation, nausea, vomiting, pruritus, dizziness and headache.

Study Design:	Randomized, double-blind, parallel-group, single-center study with two arms.
Main Inclusion Criteria:	Women, age 18-64 years, diagnosed with a benign gynecological condition, undergoing laparoscopic, supra-cervical or total hysterectomy in general anesthesia. ASA classification I-III.
Main Exclusion Criteria	<ul style="list-style-type: none"> • BMI > 31 and/or weight <55 kg, >85 kg. • Chronic pain syndromes related to organ systems other than the female reproductive system. • Chronic opioid therapy (codeine medication allowed up to 60 mg/day) or enteral steroid therapy. • Alcohol or medical abuse/addiction. • Pulmonary or neurological disease/condition known to predispose for respiratory depression. • Allergy or contraindication to any of the medications used in the study. • Lactose intolerance. • The concurrent use of monoamine oxidase inhibitors, serotonin norepinephrine reuptake inhibitors, benzodiazepines, barbiturates, neuroleptics, phenytoin tricyclic antidepressants, gabapentanoids, tramadol, clonidine, cimetidine, rifampicin, protease inhibitors, St John's wort (<i>Hypericum perforatum</i>), macrolides and antimycotics is not allowed.
Sample Size:	90 patients.
Efficacy Assessments:	Verbal pain rating by the numerical rating scale (NRS) for pain. Rating of pain relief. Global medication performance after 24 hours. Time to first rescue medicine. Total rescue analgesic consumption IV and PO over 24 hours.
Safety Assessments:	Continuous monitoring with 3-lead ECG and oxygen saturation by pulse oximetry during anesthesia and in postoperative ward. Intermittent monitoring of blood pressure, respiratory rate, measurement of end-tidal carbon dioxide and evaluation of sedation using the Pasero opioid-induced sedation scale while in postoperative ward (30, 60, 120, 180 minutes postoperatively). In the gynecological ward oxygen saturation measured by pulse oximetry, sedation using the Pasero opioid-induced sedation scale and respiratory rate will be measured at rest at 24 hours postoperatively.
Other Assessments:	Not applicable.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or special term	Explanation
AE	Adverse Event
ASA-classification	American Society of Anesthesiologists physical status classification system
BIS	Bispectral index
CRF	Case Report Form (electronic/paper)
CSA	Clinical Study Agreement
DAE	Discontinuation due to Adverse Event
ETCO ₂	End-tidal carbon dioxide
ECG	Electrocardiogram
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product (includes active comparator and placebo)
IV	Intra venous
NRS	Numerical Rating Scale for pain (range 0-10)
PO	Per oral
PRN	Pro re nata (when necessary)
REK	Regional Committees for Medical and Health Research Ethics
SAE	Serious Adverse Event
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SpO ₂	Oxygen saturation

1 INTRODUCTION

1.1 Background – Postoperative pain

In the Norwegian population about 1 out of 10 will undergo surgery every year. Most of these patients will experience postoperative pain, which initiate different measures of prophylaxis and treatment. Postoperative pain is a major cause of postoperative suffering, prolonged hospitalization, complications and increased costs. It has been shown that postoperative pain is a frequent and unresolved problem in Norwegian hospitals, and so also internationally. Building knowledge on pain prophylaxis and treatment of postoperative pain is an area with substantial potential for improvement and affecting many patients.

Opioids remain as first-line drugs for the treatment of moderate to severe postoperative pain, but the use is limited by well-known side-effects, most of which are dose-dependent. Opioids also carry an inherent risk of addiction.

1.2 Background - Therapeutic Information

The opioid oxycodone (C₁₈H₂₁NO₄. ACT: N02A A05) is used as standard therapeutic treatment for acute postoperative pain, either in immediate-release formulation, OxyNorm®, or as extended-release formulation, OxyContin®. Oxycodone is a pure opioid receptor agonist with central and peripheral effects.

Tapentadol hydrochloride/depot (Palexia/depot®; 3-dimethylamino-1-ethyl-2-methyl-propyl-phenol hydrochloride. ACT: N02A X06) is a novel, centrally acting, strong analgesic with a dual mechanism of action. It is a μ -opioid receptor agonist with central and peripheral effects, and it also inhibits noradrenaline reuptake in the central nervous system. Tapentadol is an active compound, devoid of active metabolites and not reliant on enzyme systems.(1) For these reasons, it has a low drug interaction potential.

Opioid receptors are usually not well expressed in non-inflamed peripheral tissue and they have limited effect on the peripheral pathophysiology and origin of acute wound pain. While postoperative pain basically is induced by relevant nociceptive pain nerve stimulation, there is also a neuropathic component in most cases. Opioids are not very effective in blocking neuropathic pain in low to moderate doses. Also, opioids do not have the potential to block the wind-up of pain when given before the start of surgical trauma.(2) The noradrenaline re-uptake inhibition (NRI) component of tapentadol is believed to have effect on descending pathways in the spinal cord. Such excitatory and inhibitory pathways act through monoamine systems mediated by noradrenaline and 5-hydroxytryptamine (5-HT). The inhibition of noradrenaline reuptake increases monoaminergic transmission in the descending pain inhibitory pathways, leading to reduced pain sensation. It seems like tapentadol produce not simply additive, but synergistic anti-nociceptive action by inhibitory actions in μ -opioid receptor agonism and NRI. While the effect on μ -opioid receptors is important in nociceptive pain, the NRI component seems to be especially relevant for both acute and persistent neuropathic pain.(3)

The synergistic effect of μ -opioid receptor agonism and NRI translates clinically into less adverse effects than with pure opioid agonists. This is probably due to less μ -opioid receptor stimulation.

We wish to compare the analgesic effect and side-effects of this new analgesic, tapentadol, to the standard treatment to day, oxycodone, in the acute postoperative period in patients with visceral pain.

1.3 Pre-Clinical & Clinical Experience with Tapentadol

Tapentadol has been shown effective in models of acute, osteoarthritic, neuropathic and cancer-induced bone pain.(1) There is now an increasing use of tapentadol in postoperative pain treatment in Norwegian hospitals. However, there is a lack of broad-based evidence for the use of tapentadol in the post-surgical setting. So far, to our knowledge, there are only published studies on postoperative pain treatment after orthopedic and dental surgery, but none related to visceral pain. Most studies have so far been initiated by the industry. The standard treatment today, oxycodone, on the other hand is shown in several studies to have a preferable analgesic effect on pain of visceral origin compared to morphine.(4)

The synergistic effect of μ -opioid receptor agonism and NRI translates clinically into less adverse effects than with pure opioid agonists. Tapentadol is shown in several studies on chronic pain patients to have comparable analgesic effects to

traditional opioid pain medications like oxycodone and morphine, but with a more tolerable side effect profile. In the postoperative setting after dental or orthopedic surgery, studies have shown less nausea and constipation. (5-7) It has also been suggested a lower frequency of pruritus compared with oxycodone, but no difference in central nervous system symptoms such as somnolence or dizziness.(8) The most dangerous side-effect from opioids is respiratory depression with the potential of fatal outcome.(9) Intravenous oxycodone is shown to have dose dependent effect on respiratory depression decreasing the mean minute volume with a more rapid onset than morphine.(10) One study has attempted to study respiratory depression after tapentadol administration, but failed due to technical failure of the pulse oximetry device.(5) We have not found any other publications from short-term postoperative pain management comparing any respiratory effect of tapentadol to the traditional opioids.(11)

1.4 Rationale for the Study and Purpose

Patients scheduled for elective hysterectomy are chosen as our study population, as this is a group of patients with significant visceral pain after surgery. The comparator, oxycodone, is the standard opioid used for treatment of acute postoperative pain in these patients today. Oxycodone, as all other opioids, has known side-effects such as nausea, vomiting, constipation, pruritus, somnolence and respiratory depression which pose potential risks or discomfort to the patients. From previous clinical studies in orthopedic and dental patients we know that tapentadol probably has an equal analgesic potential to oxycodone, but with less side-effects (best evidence for gastrointestinal side-effects).(5-7) However, there are no studies done on respiratory depression from tapentadol which may be the most dangerous risk to the patients.(5,11) Showing less respiratory depression from tapentadol, but equal analgesic effect to comparable opioids, would be of immense benefit to the patient population as this would eliminate or reduce the most dangerous and potentially fatal side-effect from opioids. Overall, less side-effects from opioids may result in less complications and shorter in-hospital admissions. In terms of patient comfort (both physically and mentally), less side-effects are of significance as previous studies have shown that patients will accept some level of pain if opioid side-effects such as nausea, vomiting, constipation and pruritus are reduced.

For the individual patient in the study receiving tapentadol there is a possible benefit in experiencing better analgesic effect and less side-effects, and on the other hand the individual patient receiving oxycodone may experience an inferior analgesic treatment and more side-effects. It is however also possible that tapentadol may result in an inferior pain treatment and/or increase in less common opioid related side-effects such as headache. A general benefit to the study population may be closer follow-up in terms of postoperative pain treatment.

We will perform a randomized, double-blind, prospective, parallel-group, single-center study on patients scheduled for laparoscopic sub-/total hysterectomy, as this is a classic study comparing effects from two different medications on two groups in a population.

Dosing is based on the previous clinical studies done on orthopedic and dental surgery patients, showing an approximate 1:5 correlation between oral oxycodone and tapentadol. (11,12) In standard postoperative pain treatment today, OxyContin 10 mg has an extended-release effect and is used as part of premedication. It is further administered twice daily. OxyNorm 10 mg has an immediate-release effect and is commonly used as rescue medicine in the postoperative period. We have therefore chosen Palexia depot 50 mg as part of premedication and to be administered once more during the study period. Palexia 50 mg will be used as rescue medicine as the equivalent to OxyNorm.

2 STUDY OBJECTIVES AND RELATED ENDPOINTS

The primary goal of our study is to examine the analgesic effect in patients receiving either tapentadol or oxycodone during the first 24 hours postoperatively after hysterectomy. As a secondary goal, we want to examine the respiratory depressive effect from tapentadol compared to oxycodone. Further, we will also examine other common opioid related side-effects: sedation, nausea, vomiting, pruritus, dizziness and headache.

2.1 Primary Endpoint

Difference in scoring of pain using the numerical rating scale (NRS) between the two groups 1 hour postoperatively.

The patient will be asked to score their pain intensity by a standardized question for the NRS: “Hvor sterk er smerten din nå på en skala fra 0 til 10, når 0 er ingen smerte og 10 er verst tenkelig smerte?”

2.2 Secondary Endpoints

- **Pain:**

Baseline pain measured with NRS is done 15 minutes after extubation.

Pain at rest and while coughing, measured with NRS, is registered at 30 minutes, 1, 2, 3 and 24 hours postoperatively. Pain intensity difference (PID) at rest at 30 minutes, 1, 2, 3 and 24 hours will be calculated from these values. Sum of pain intensity difference (SPID) at 24 hours is calculated as the time-weighted sum of the PID scores ($SPID\ t = \sum PID \times (time\ t - time\ t-1)$).

Pain relief, measured with categorical scale “none, slight, moderate, good or complete”, at 30 minutes, 1, 2, 3 and 24 hours postoperatively. Total pain relief (TOTPAR) over 24 hours will be calculated from these values.

Worst pain during 24 hours is measured with NRS.

Global medication performance (GMP) after 24 hours: “poor, fair, good, very good, excellent”.

Time to first rescue medicine (IV and/or PO) and total rescue analgesic consumption IV and PO over 24 hours is also registered.

- **Respiratory depression:**

In the postoperative ward: continuous measurement of ETCO₂ with Smart CapnoLine® Plus (Microstream®), data are collected at 30, 60, 120, 180 minutes postoperatively. Respiratory rate at rest is measured at 30, 60, 120, 180 minutes postoperatively. Any episodes of ETCO₂ > 7.0 or respiratory rate < 10 are also recorded.

In the gynecological ward: oxygen saturation measured by pulse oximetry and respiratory rate measured at rest at 24 hours postoperatively.

- **Sedation:**

Sedation is evaluated at 30 minutes and 1, 2, 3 and 24 hours postoperatively, using the Pasero opioid-induced sedation scale.

Table 1. Pasero Opioid-induced Sedation Scale (POSS) With Interventions*

S = Sleep, easy to arouse
<i>Acceptable; no action necessary; may increase opioid dose if needed</i>
1. Awake and alert
<i>Acceptable; no action necessary; may increase opioid dose if needed</i>
2. Slightly drowsy, easily aroused
<i>Acceptable; no action necessary; may increase opioid dose if needed</i>
3. Frequently drowsy, arousable, drifts off to sleep during conversation
<i>Unacceptable; monitor respiratory status and sedation level closely until sedation level is stable at less than 3 and respiratory status is satisfactory; decrease opioid dose 25% to 50%¹ or notify prescriber² or anesthesiologist for orders; consider administering a non-sedating, opioid-sparing nonopioid, such as acetaminophen or an NSAID, if not contraindicated.</i>
4. Somnolent, minimal or no response to verbal or physical stimulation
<i>Unacceptable; stop opioid; consider administering naloxone^{3,4}; notify prescriber² or anesthesiologist; monitor respiratory status and sedation level closely until sedation level is stable at less than 3 and respiratory status is satisfactory.</i>

- **Nausea:** yes/no at 30 minutes and 1, 2, 3 and 24 hours postoperatively.
- **Vomiting:** yes/no at 30 minutes and 1, 2, 3 and 24 hours postoperatively.
- **Pruritus:** yes/no at 30 minutes and 1, 2, 3 and 24 hours postoperatively.
- **Dizziness:** yes/no at 30 minutes and 1, 2, 3 and 24 hours postoperatively.
- **Headache:** yes/no at 30 minutes and 1, 2, 3 and 24 hours postoperatively.

3 OVERALL STUDY DESIGN

The study is a phase IV study.

This is a randomized, double-blind, prospective, parallel-group, single-center study on patients scheduled for laparoscopic sub-/total hysterectomy.

Study Period Estimated date of first patient enrolled: 01.09.17.

Anticipated recruitment period: 1 year 6 months.

Estimated date of last patient completed: 01.03.19.

Treatment Duration: 24 - 32 hours (depending on last administration of PRN).

Follow-up: End of treatment visit in person at 24 hours. Last contact is made by telephone at 32 hours. No further follow-ups.

4 STUDY POPULATION

4.1 Selection of Study Population

The study will be conducted at Oslo University Hospital in Oslo, Norway.

4.2 Number of Patients

90 patients will be included in this trial.

4.3 Inclusion Criteria

- Women diagnosed with a benign gynecological condition, undergoing laparoscopic, supra-cervical or total hysterectomy in general anesthesia.
- Age 18-64 years.
- ASA classification I-III.
- Signed informed consent and expected cooperation of the patients for the treatment and follow up must be obtained and documented according to ICH GCP, and national/local regulations.
- The patients will be recruited from the patient population at the Department of Gynaecology.

4.4 Exclusion Criteria

- Age under 18 or over 65.
- BMI > 31 and/or weight <55 kg, >85 kg.
- Chronic pain syndromes related to organ systems other than the female reproductive system.
- Chronic opioid therapy (codeine medication allowed up to 60 mg/day) or enteral steroid therapy.
- Alcohol or medical abuse/addiction.
- Chronic obstructive pulmonary disease (spirometry with postbronchodilator FEV₁/FVC ratio less than 0.7), untreated asthma (FEV₁/FVC is reduced to less than 0.70), obstructive sleep apnea or other conditions known to predispose for respiratory depression.
- Neurological diagnosis with affection of respiratory system or prone to seizures.
- Previously diagnosed kidney (glomerular filtration rate <60 mL/min/1.73 m² over 3 months) or liver impairment (ALAT > 45 U/L; ASAT > 35 U/L; ALP > 105 U/L; GT > 45 U/L age 18-39 or GT > 75 U/L age over 39; LD > 205 U/L).
- Biliary tract disease.
- Paralytic ileus.
- Heart failure (NYHA III-IV).
- Malignancy of any kind under treatment. Malignancy during last 5 years.
- HIV infection. Infections of any kind affecting the patient's clinical status, i.e. upper or lower airway infection, urinary tract infection, deep wound infection. Infections not affecting the patient's clinical status, i.e. conjunctivitis, is not an exclusion criteria.
- Untreated depression, severe anxiety or other psychiatric disorders independent of treatment.
- Nursing mothers.
- Cognitive failure, language barriers, hearing/visual disability or other factors which make follow-up difficult.
- Allergy or contraindication to any of the medications used in the study.
- Lactose intolerance.
- Monoamine oxidase inhibitors or SNRI (serotonin norepinephrine reuptake inhibitors) within 14 days prior to randomization. SSRI (selective serotonin reuptake inhibitors) use is not an exclusion criterion if stable dose for at least 30 days before screening.
- H1-antihistamine is not an exclusion criterion unless the patient experiences somnolence as a side-effect.
- The concurrent use of benzodiazepines, barbiturates, neuroleptics, phenytoin tricyclic antidepressants, gabapentanoids, tramadol, clonidine, cimetidine, rifampicin, protease inhibitors, St John's wort (*Hypericum perforatum*), macrolides and antimycotics such as ketoconazole and fluconazole are not allowed.
- Known complications to anesthesia or difficult airway (Definition of difficult airway: "The clinical situation in which a conventionally trained anesthesiologist experiences difficulty with mask ventilation, difficulty with tracheal intubation, or both.").
- Patients who have participated in other clinical trials during the last 6 months are excluded to avoid confounders to the current study and for patient safety reasons.

5 TREATMENT

For this study tapentadol (Palexia®, Palexia depot®) and the active comparator oxycodone (OxyContin®, OxyNorm®) are defined as Investigational Medicinal Products (IMP).

5.1 Drug Identity, Supply and Storage

- Palexia 50 mg® (Tapentadol 50 mg): Tablet, immediate-release, ATC-nr N02A X06. (Grünenthal Norway AS)
- Palexia depot 50 mg® (Tapentadol depot 50 mg): Tablet, extended-release, ATC-nr N02A X06. (Grünenthal Norway AS)
- OxyNorm 10 mg® (Oxycodone immediate-release 10 mg): Capsule, immediate-release, ATC-nr N02A A05. (Mundipharma AS, Norway)

- OxyContin 10 mg® (Oxycodone extended-release 10 mg): Tablet, extended-release, ATC-nr N02 A05. (Mundipharma AS, Norway)

All four drugs can be stored in room temperature and are not light or temperature sensitive.

The drugs will be distributed to the patients in pill box organizers. The pill box organizers will be packed by one of the study investigators, Harald Lenz, who will not otherwise participate in the handling of the patients. The packing and labeling will be double-checked by another nurse or doctor not involved in the study to ensure hospital standards for drug dispensing. See appendix A for instruction on how to pack and label the study medicine.

The pill box organizer will be stored according to Oslo University Hospital guidelines for narcotics before distribution (locked storage room for medicines, nurse-only access). The pill box organizer must follow the patient to the postoperative ward for access to PRN medication. While in the postoperative ward and the gynecological ward the patient is expected to administer her own pain medication from the pill box organizer, but for safety reasons the pill box organizer will be stored by the ward nurse. The nurse will provide the pill box organizer upon the patients request and the patient will administer the medication from the pill box organizer herself. This ensures the recording of all medication in the patient's medicinal chart at all times.

5.2 Dosage and Drug Administration

The drugs will be distributed to the patients in pill box organizers in sealed, opaque envelopes by a ward nurse at the time of premedication. A detailed written instruction and form for self-administration of the study medication is provided (see appendix B). Verbal instruction will also be given by the investigator and a sham pill box organizer will be shown to the patient to help illustrate which medication to use when. The patient is required to note times of administration of study medicine in the form for safety and study purposes. The instruction/form and pill box must follow the patient at all times during the first day of surgery.

- Palexia depot 50 mg® (tapentadol depot 50 mg): Administered by the patient as oral premedication 1 hour before scheduled start of surgery. The ward nurse will administer the rest of the premedication simultaneously. Palexia depot is repeated once after 12 hours.
 - Palexia 50 mg® (tapentadol 50 mg): Administered as oral PRN. First possible administration in postoperative ward when the patient is awake and available for oral medication. Maximum 4 tablets/24-hour study period. Minimum 1 hour 15 minutes between tablets. The patient is instructed to take 1 tablet if pain is increasing and the minimum period since last tablet is exceeded.
- or
- OxyContin 10 mg® (oxycodone extended-release 10 mg): Administered by the patient as oral premedication 1 hour before scheduled start of surgery. The ward nurse will administer the rest of the premedication simultaneously. OxyContin is repeated once after 12 hours.
 - OxyNorm 10 mg® (oxycodone immediate-release 10 mg): Administered as oral PRN. First possible administration in postoperative ward when the patient is awake and available for oral medication. Maximum 4 capsules/24-hour study period. Minimum 1 hour 15 minutes between capsules. The patient is instructed to take 1 tablet if pain is increasing and the minimum period since last tablet is exceeded.

Concerning PRN medication:

In the *postoperative ward* rescue analgesic will be available according to type of study medicine:

PRN: tapentadol 50 mg PO or oxycodone IR 10 mg PO according to randomization. Maximum total dose tapentadol (including PRN medication)/24 hours: 300 mg. Maximum total dose oxycodone (including PRN medication)/24 hours: 60 mg.

If urgent pain relief is needed oral medication is not always sufficient or feasible, fentanyl 1 microgram/kg IV will therefore be available as rescue analgesic medication the first postoperative hours. Fentanyl is also the drug of choice if postoperative shivering occurs. Fentanyl is standard postoperative pain treatment and not considered part of study medicine.

In the *gynecological ward* the patients will have the opportunity to administer additional doses of study medicine as rescue medicine during the 24-hour study period:

PRN: tapentadol 50 mg PO or oxycodone IR 10 mg PO according to randomization. Maximum total dose tapentadol (including PRN medication)/24 hours: 300 mg. Maximum total dose oxycodone (including PRN medication)/24 hours: 60 mg.

In addition to Arcoxia® (etorikoksib) 120/90 mg PO and Paracet® (paracetamol) premedication 2.0/1.5 g, the patients will also receive paracetamol 1 g x 3 PO during the 24-hour study period. This is part of standard postoperative pain treatment and is administered by the ward nurses.

The study treatment will be dispensed to the subject by authorized site personnel only.

The choice of PRN oxycodone dose, OxyNorm 10 mg PO, is based on previous studies done by our study group.(13, 14) In a similar patient group (laparoscopic hysterectomy in women) the postoperative opioid consumption of intravenous oxycodone versus morphine was examined. A mean need of 13.3 ± 10.4 mg oxycodone IV was accumulated over 24 hours. Converted to PO oxycodone (conversion rate of 2.2) this is approximately 29.3 ± 22.9 mg oxycodone PO/24 h.(13) In the second study with a similar patient group the postoperative consumption of oxycodone versus oxycodone+naloxone was examined. A mean need of 20 mg PO oxycodone + 19 mg IV oxycodone PRN was found over 24 hours. Converted to PO oxycodone this amounts to 61.8 mg/24 h.(14) We have therefore chosen the dosage of OxyNorm 10 mg PO up to 4 times a day in addition to OxyContin 10 mg x 2 to ensure the need of up to 61.8 mg oxycodone during 24 hours.

In accordance to standard pain treatment procedures the PRN medication will be administered with an interval of minimum 1,25 h.

5.3 Duration of Therapy

- Palexia depot 50 mg® (Tapentadol depot 50 mg): $t_{1/2}$ 5-6 hours, last time of administration at 12 hours after study start. Expected duration of therapy 24 hours.
- Palexia 50 mg® (Tapentadol 50 mg): $t_{1/2}$ 4 hours, last possible time of administration at 24 hours after study start. Expected duration of therapy 8 hours after last time of administration.
- OxyContin 10 mg® (Oxycodone extended-release 10 mg): $t_{1/2}$ 4,5 hours, estimated effect time 12 hours according to SmPC, last time of administration 12 hours after study start. Expected duration of therapy 24 hours.
- OxyNorm 10 mg® (Oxycodone immediate-release 10 mg): $t_{1/2}$ 3 hours, estimated effect time 6 hours according to SmPC, last possible time of administration at 24 hours after study start. Expected duration of therapy 6 hours after last time of administration.

In summary, expected therapy duration is minimum 24 hours. If immediate-release medication (Palexia® or OxyNorm®) is administered at 24 hours after study start, the duration of treatment is expected to extend for a further 6-8 hours. End of treatment is therefore set to 32 hours after first dose at premedication.

5.4 Premedication and Monitoring

Premedication:

Administered 1 hour before surgery: Paracet® (paracetamol) 2/1.5 g PO and Arcoxia® (etorikoksib) 120/90 mg PO (according to weight limit 60 kg and age limit 60 years). This is part of standard pain treatment and will be administered by the ward nurses. Study medication according to randomization: tapentadol depot 50 mg PO or oxycodone ER 10 mg PO. The study medication will be self-administered by the patient.

The patient is allowed to take any regular medication, but with restrictions according to anesthesia standards.

The patient must be fasting prior to general anesthesia according to anesthesia standards (6 hours for food and 2 hours for clear liquids or smoking).

Monitoring:

Pre- and perioperative data:

Vital sign assessment (blood pressure and pulse) is registered preoperatively.

Continuous ECG, BIS, heart rate, ETCO₂ and SpO₂ measurement throughout the perioperative period. Minimum/maximum blood pressures are registered.

Target measures and interventions:

Blood pressure: systolic 80-120 mmHg. Intervention low pressures: Efedrin® (efedrin) 5-10 mg IV. Intervention high pressures: increase propofol and/or remifentanyl at the discretion of the anesthetist.

Heart rate: 45-90. Intervention if bradycardia: Atropin® (atropin) 0.4-1 mg IV or efedrin® 5-10 mg IV at the discretion of the anesthetist. Intervention if tachycardia: at the discretion of the anesthetist.

SpO₂: > 94%. Intervention at the discretion of the anesthetist.

BIS: 40-55. Intervention at the discretion of the anesthetist.

Postoperative data:

Time is defined from time of emergence from anesthesia (time zero), and the time intervals are referred to as "postoperatively".

In the postoperative ward: Continuous monitoring with 3-lead ECG and oxygen saturation by pulse oximetry. Intermittent monitoring of blood pressure at 30, 60, 120 and 180 minutes postoperatively. Recording of all values in CRF at 30, 60, 120 and 180 minutes postoperatively. Continuous measurement of ETCO₂ with Smart CapnoLine® Plus (Microstream®), data are collected at 30, 60, 120, 180 minutes postoperatively. Respiratory rate at rest is measured at 30, 60, 120, 180 minutes postoperatively. Any episodes of ETCO₂ > 7.0 or respiratory rate < 10 are also recorded.

In the gynecological ward: oxygen saturation measured by pulse oximetry and respiratory rate measured at rest at 24 hours postoperatively. Blood pressure and pulse are measured according to standard ward procedures.

5.5 Concomitant Medication

All concomitant medication (incl. vitamins, herbal preparation and other "over-the-counter" drugs) used by the patient and the following medications as part of general anesthesia, pre- and postoperative treatment will be recorded in the patient's file and CRF.

Premedication:

- Paracet® (paracetamol) 2/1.5 g PO (according to weight limit 60 kg and age limit 60 years).
- Arcoxia® (etorikoksib) 120/90 mg PO (according to weight limit 60 kg and age limit 60 years).

General anesthesia:

- Propolipid® (propofol) target controlled infusion for both induction and maintenance of anesthesia.
- Ultiva® (remifentanyl) target controlled infusion for both induction and maintenance of anesthesia.
- If a muscle relaxant is needed for intubation Nimbex® (cisatrakurium) 0.1-0.15 mg/kg IV is administered.
- Dexamethason® (deksametason) 8 mg IV is administered at the beginning of anesthesia.
- Zofran® (ondansetron) 4 mg IV is administered towards end of anesthesia.
- Fentanyl® (fentanyl) 1 microgram/kg IV is administered 10 minutes prior to end of general anesthesia.
- By the end of surgery the incision sites will be injected with a total of 20 ml Marcain® (bupivakain) 2.5 mg/ml.
- Intervention if low blood pressures: Efedrin® (efedrin) 5-10 mg IV.
- Intervention if bradycardia: Atropin®(atropin) 0.4-1 mg IV or efedrin® 5-10 mg IV at the discretion of the anesthetist.

Postoperative ward:

If urgent pain relief is needed, fentanyl 1 microgram/kg IV will be available as rescue analgesic medication the first postoperative hours. Fentanyl is also the drug of choice if postoperative shivering occurs.

Postoperatively (postoperative and/or gynecological ward):

In addition to paracetamol premedication 2.0/1.5 g the patients will also receive paracetamol 1 g x 3 PO during the 24-hour study period.

If nausea and/or vomiting:

- Afipran® (metoklopramid) 10 mg IV, maximum dose 30 mg/24 hours.
- If no effect within 10 minutes from afipran 10 mg IV, zofran 4 mg IV may be administered if more than 4 hours since previous zofran dose.
- Dridol® (droperidol) 0.625 mg IV may be administered at the tending physician's discretion if no effect from the previous medications.

Prohibited medication:

- Monoamine oxidase inhibitors or SNRI (serotonin norepinephrine reuptake inhibitors) within 14 days prior to randomization. (SSRI (selective serotonin reuptake inhibitors) use is not prohibited if stable dose for at least 30 days before screening.)
- H1-antihistamine is prohibited if the patient experiences somnolence as a side-effect.
- The concurrent use of benzodiazepines, barbiturates, neuroleptics, phenytoin tricyclic antidepressants, gabapentanoids, tramadol, clonidine, cimetidine, rifampicin, protease inhibitors, St John's wort (*Hypericum perforatum*), macrolides and antimycotics such as ketoconazole and fluconazole is not allowed.
- Opioids, non-steroidal anti-inflammatory drugs or steroids other than those mentioned in this protocol.

5.6 Subject Compliance

A detailed written instruction and form for self-administration of the study medication is provided along with the pill box organizers (see appendix B). Verbal instruction on how to take the study medicine will also be given by the investigator at the time of inclusion. A sham pill box organizer will be shown to the patient to help illustrate which medication to use when. (The envelopes with pill box organizers and instructions for use will be given to the patients at the time of premedication by a ward nurse not participating in the study, thus blinding the researchers to the patients' allocation.)

The patient is required to note times of administration of study medicine in the form for safety and study purposes. The instruction/form and pill box must follow the patient at all times during the first day of surgery. The instruction will also ensure that the ward nurses know the patient is part of a study and the nurse may assist the patient accordingly if needed. Investigators will be at hand for questions from both the patient and the staff.

The times for study medicine taken, including PRN medication, must also be noted in the patient's medication chart as part of standard hospital procedures. This will be done by the ward nurses.

The pill box organizers are collected at the 24-hour visit and are available for pill count by Harald Lenz before disposing.

5.7 Drug Accountability

The responsible site personnel will confirm receipt of study drug and will use the study drug only within the framework of this clinical study and in accordance with this protocol. Receipt, distribution, return, and destruction (if any) of the study drug must be properly documented according to the sponsor's agreed and specified procedures.

Identical pill box organizers will be filled with the respective study medicines, either tapentadol depot 50 mg (Palexia depot®) or oxycodone extended release (OxyContin®) 10 mg and rescue medicine which is either tapentadol 50 mg (Palexia®) or oxycodone immediate release (OxyNorm®) 10 mg. This will be done by one of the investigators, Harald Lenz, and a nurse anesthetist not participating in the study. Harald Lenz will not participate in the inclusion or other handling of patients to ensure blinding. The nurse anesthetist has experience with drug dispensing as part of his daily tasks. This procedure ensures hospital standards of double checking medication before administration. The personnel packing and labeling the pill box dispenser will both sign a log (a batch manufacturing record) for each of the individual pill box dispenser assigned to a patient. The pill box organizers will have unique serial numbers to connect them to the accompanying self-administration log.

The study drugs, will be distributed in the pill box organizers which are pre-packed in identical, opaque envelopes. The envelopes are not to be broken until randomization of the patient is done. These envelopes with instructions for use will be given to the patients at the time of premedication by a ward nurse not participating in the study, thus blinding the researchers to the patients' allocation. While in the postoperative ward and the gynecological ward the patient is expected to administer her own pain medication from the pill box organizer, but for safety reasons the pill box organizer will be stored by the ward nurse. The nurse will provide the pill box organizer upon the patients request and the patient will administer the medication from the pill box organizer herself. This also maintains blinding of the study investigators doing pain assessments.

The pill box organizer will be stored according to Oslo University Hospital guidelines for narcotics before distribution (locked storage room for medicines, nurse-only access). The pill box organizer must follow the patient to the postoperative ward for access to PRN medication. In the gynecological ward the nurse will provide the pill box organizer upon the patients request and the patient will administer the medication from the pill box organizer herself.

The pill box organizers are collected at the 24-hours visit and put in sealed, opaque bags. Any remaining study medicine will be logged in the CRF by Harald Lenz before being disposed of according to hospital standards.

5.8 Drug Labeling

The investigational product will have a label permanently affixed to the outside and will be labeled according with ICH GCP and national regulations, stating that the material is for clinical trial / investigational use only and should be kept out of reach of children.

Labeling of the IMPs will be done by one of the investigators, Harald Lenz, and a nurse anesthetist not participating in the study.

The labeling will be in Norwegian. One label is attached to the pill box organizer with the most critical information: pill box organizer serial number; "Til klinisk utprøving"; Oppbevares utilgjengelig for barn; Se vedlagt bruksanvisning. See pictures:



Due to space limitations further labeling is included in the instructions/form accompanying the pill box organizer. The instructions/form and pill box organizer will have identical identifying numbers.

The instructions/form will include the following labeling (see also appendix B):

- Patient's enrolment code
- Patient's initials
- Date dispensed
- Instructions/form unique identity number (same as number on pill box organizer)
- Protocol code
- Batch number
- Date for packing and labeling of study medicine with signatures
- Expiration date
- Name of prescribing doctor
- Name of Principal Investigator
- Contact information to three of the investigators.

5.9 Subject Numbering

Each subject is identified in the study by a unique subject number (nr XX) that is assigned when subject signs the Informed Consent Form. A record in the clinical study file will keep track of the next number to assign. Once assigned the subject number cannot be reused for any other subject.

6 STUDY PROCEDURES

6.1 Flow Chart

	Screening Period	Treatment Period										End of treatment visit
Time	1-14 days prior to treatment	Premedication	Anesthesia/Surgery	15 min postopr	30 min postopr	60 min postopr	120 min postopr	180 min postopr	6 hours after premedication	12 hours after premedication	18 hours after premedication	24 hours after premedication
Inclusion/exclusion evaluation	X											
Informed consent	X											
Questionnaire	X											
Treatment administration		X								X		
PRN medication (possible times of administration, but not limited to)				X	X	X	X	X	X	X	X	
Concomitant medication		X	X						X	X	X	
Vital signs			X		X	X	X	X				X
Pain assessment				X	X	X	X	X				X
Respiratory assessment					X	X	X	X				X
Adverse event (possible times of events, but not limited to)			X	X	X	X	X	X	X	X	X	X
Abbreviations: PRN: pro re nata (when necessary) Postopr: postoperatively												

6.2 By Visit

Informed consent

Informed consent must have been given voluntarily by each subject before any study specific procedures are initiated. The following tests will be done at screening:

Clinical status

Medical history, physical examination (cor/pulm/gynecological examination), vital signs (weight, height, blood pressure and pulse) is collected by the gynecologist in the outpatient clinic upon decision for surgery. Physical examination and vital sign may be collected on the day of surgery for patients if they have not been to the outpatient clinic beforehand.

Concomitant medication

All concomitant medication (incl. vitamins, herbal preparation and other “over-the-counter” drugs) used by the subject within 28 days of treatment start and the following medications as part of general anesthesia, pre- and postoperative treatment will be recorded in the patient’s file and CRF.

Premedication:

- Paracet® (paracetamol) 2/1.5 g PO (according to weight limit 60 kg and age limit 60 years).
- Arcoxia® (etorikoksib) 120/90 mg PO (according to weight limit 60 kg and age limit 60 years).

General anesthesia:

- Propolipid® (propofol) target controlled infusion for both induction and maintenance of anesthesia.
- Ultiva® (remifentanyl) target controlled infusion for both induction and maintenance of anesthesia.
- If a muscle relaxant is needed for intubation Nimbex® (cisatrakurium) 0.1-0.15 mg/kg IV is administered.
- Dexamethason® (deksametason) 8 mg IV is administered at the beginning of anesthesia.
- Zofran® (ondansetron) 4 mg IV is administered towards end of anesthesia.
- Fentanyl® (fentanyl) 1 microgram/kg IV is administered 10 minutes prior to end of general anesthesia.
- By the end of surgery the incision sites will be injected with a total of 20 ml Marcain® (bupivakain) 2.5 mg/ml.
- Intervention if low blood pressures: Efedrin® (efedrin) 5-10 mg IV.
- Intervention if bradycardia: Atropin®(atropin) 0.4-1 mg IV or efedrin® 5-10 mg IV at the discretion of the anesthetist.

Postoperative ward:

If urgent pain relief is needed, fentanyl 1 microgram/kg IV will be available as rescue analgesic medication the first postoperative hours. Fentanyl is also the drug of choice if postoperative shivering occurs.

Postoperatively (postoperative and/or gynecological ward):

In addition to paracetamol premedication 2.0/1.5 g the patients will also receive paracetamol 1 g x 3 PO during the 24-hour study period.

If nausea and/or vomiting:

- Afipran® (metoklopramid) 10 mg IV, maximum dose 30 mg/24 hours.
- If no effect within 10 minutes from afipran 10 mg IV, zofran 4 mg IV may be administered if more than 4 hours since previous zofran dose.
- Dridol® (droperidol) 0.625 mg IV may be administered at the tending physician's discretion if no effect from the previous medications.

6.2.1 Before Treatment Starts

The patients will be selected from the scheduled operation program. They have by then been to a consultation with a gynecologist in the outpatient clinic. Medical history, list of concomitant medications, allergies, smoking, physical examination and vital signs are collected by the gynecologist as part of standard procedure before surgery. Some patients travelling from other parts of Norway may have this consultation done the same day as surgery.

If the patient is found eligible for inclusion in the study based on the information available in the patient journal system, an investigator (Marlin Comelon) will assess the patient according to the ASA-classification system. If the patient is ASA I-III and suitable for general anesthesia the patient will be contacted by letter, phone or in person (if already admitted to the hospital) depending on time until surgery. Patient information about the study and a questionnaire concerning predisposing factors for postoperative pain (Appendix C) are distributed to the patient in paper form. The patient signs an informed consent form if she decides to participate in the study. Study investigators Marlin Comelon, Johan Ræder or Tomas Drægni will see the patient in person on the day of surgery for questions about the study and to collect the informed consent form. Information about previous anesthesia such as postoperative nausea and vomiting or complications will be then registered. An anesthesiologist not connected to the study will also perform a regular pre-anesthesia visit.

6.2.2 During Treatment

Time is defined from time of emergence from anesthesia (time zero), and the time intervals are referred to as "postoperatively".

Perioperatively/Anesthesia procedure and monitoring:

Premedication according to standard treatment is administered 1 hour before surgery: Paracet® (paracetamol) 2/1.5 g PO and Arcoxia® (etorikoksib) 120/90 mg PO (according to weight limit 60 kg and age limit 60 years). Study medication according to randomization is administered at time of premedication: tapentadol depot 50 mg PO or oxycodone ER 10 mg PO.

The surgery will be conducted in general anesthesia using target controlled infusion of Propolipid® (propofol) and Ultiva® (remifentanyl) for both induction and maintenance of anesthesia. The patients have assisted normoventilation via a tracheal tube or laryngeal mask airway. If a muscle relaxant is needed for intubation Nimbex® (cisatracurium) 0.1-0.15 mg/kg IV is administered. Dexamethason® (deksametason) 8 mg IV is administered at the beginning of anesthesia. Zofran® (ondansetron) 4 mg IV is administered towards end of anesthesia. Fentanyl® (fentanyl) 1 microgram/kg IV is administered 10 minutes prior to end of general anesthesia. By the end of surgery the incision sites will be injected with a total of 20 ml Marcain® (bupivakain) 2.5 mg/ml.

Data registered for surveillance of general anesthesia and study purposes (safety; not study end-points):

Vital sign assessment (blood pressure and pulse) is registered preoperatively.

Continuous ECG, BIS, heart rate, ETCO₂ and SpO₂ measurement throughout the perioperative period.
Minimum/maximum blood pressures are registered.

Type of surgery, surgery time, anesthesia time. Propofol dose, remifentanyl dose, dexamethasone, ondansetron, metoclopramide, other medications.

Target measures:

Blood pressure: systolic 80-120 mmHg. Intervention low pressures: Efedrin® (efedrin) 5-10 mg IV. Intervention high pressures: increase propofol and/or remifentanyl at the discretion of the anesthetist.

Heart rate: 45-90. Intervention if bradycardia: Atropin®(atropin) 0.4-1 mg IV or efedrin® 5-10 mg IV at the discretion of the anesthetist. Intervention if tachycardia: at the discretion of the anesthetist.

SpO₂: > 94%. Intervention at the discretion of the anesthetist.

BIS: 40-55. Intervention at the discretion of the anesthetist.

Postoperative procedure and monitoring:

In the postoperative ward rescue analgesic will be available according to type of study medicine:

PRN: tapentadol 50 mg PO or oxycodone IR 10 mg PO according to randomization. Maximum total dose tapentadol (including PRN medication)/24 hours: 300 mg. Maximum total dose oxycodone (including PRN medication)/24 hours: 60 mg.

If urgent pain relief is needed, fentanyl 1 microgram/kg IV will be available as rescue analgesic medication the first postoperative hours. Fentanyl is also the drug of choice if postoperative shivering occurs.

In the gynecological ward the patients will have the opportunity to administer additional doses of study medicine as rescue medicine during the 24-hour study period:

PRN: tapentadol 50 mg PO or oxycodone IR 10 mg PO according to randomization. Maximum total dose tapentadol (including PRN medication)/24 hours: 300 mg. Maximum total dose oxycodone (including PRN medication)/24 hours: 60 mg.

In addition to paracetamol premedication 2.0/1.5 g the patients will also receive paracetamol 1 g x 3 PO during the 24-hour study period. This is part of standard postoperative pain treatment.

Continuous monitoring with 3-lead ECG and oxygen saturation by pulse oximetry while in postoperative ward. Intermittent monitoring of blood pressure at 30, 60, 120 and 180 minutes postoperatively. Recording of all values in CRF at 30, 60, 120 and 180 minutes postoperatively.

Data registered:

Pain:

Baseline pain measured with NRS is done 15 minutes after extubation.

Pain at rest and while coughing, measured with NRS, is registered at 30 minutes, 1, 2, 3 and 24 hours postoperatively. Pain intensity difference (PID) at rest at 30 minutes, 1, 2, 3 and 24 hours will be calculated from

these values. Sum of pain intensity difference (SPID) at 24 hours is calculated as the time-weighted sum of the PID scores ($SPID\ t = \sum PID \times (time\ t - time\ t-1)$).

Pain relief, measured with categorical scale “none, slight, moderate, good or complete”, at 30 minutes, 1, 2, 3 and 24 hours postoperatively. Total pain relief (TOTPAR) over 24 hours will be calculated from these values.

Worst pain during 24 hours is measured with NRS.

Global medication performance (GMP) after 24 hours: “poor, fair, good, very good, excellent”.

Time to first rescue medicine (IV and/or PO) and total rescue analgesic consumption IV and PO over 24 hours is also registered.

Respiratory depression:

In the postoperative ward: continuous measurement of ETCO₂ with Smart CapnoLine® Plus (Microstream®), data are collected at 30, 60, 120, 180 minutes postoperatively. Respiratory rate at rest is measured at 30, 60, 120, 180 minutes postoperatively. Any episodes of ETCO₂ > 7.0 or respiratory rate < 10 are also recorded.

In the gynecological ward: oxygen saturation measured by pulse oximetry and respiratory rate measured at rest at 24 hours postoperatively.

Sedation:

Sedation is evaluated at 30 minutes and 1, 2, 3 and 24 hours postoperatively, using the Pasero opioid-induced sedation scale.

Table 1. Pasero Opioid-induced Sedation Scale (POSS) With Interventions*

S = Sleep, easy to arouse
<i>Acceptable; no action necessary; may increase opioid dose if needed</i>
1. Awake and alert
<i>Acceptable; no action necessary; may increase opioid dose if needed</i>
2. Slightly drowsy, easily aroused
<i>Acceptable; no action necessary; may increase opioid dose if needed</i>
3. Frequently drowsy, arousable, drifts off to sleep during conversation
<i>Unacceptable; monitor respiratory status and sedation level closely until sedation level is stable at less than 3 and respiratory status is satisfactory; decrease opioid dose 25% to 50%¹ or notify prescriber² or anesthesiologist for orders; consider administering a non-sedating, opioid-sparing nonopioid, such as acetaminophen or an NSAID, if not contraindicated.</i>
4. Somnolent, minimal or no response to verbal or physical stimulation
<i>Unacceptable; stop opioid; consider administering naloxone^{3,4}; notify prescriber² or anesthesiologist; monitor respiratory status and sedation level closely until sedation level is stable at less than 3 and respiratory status is satisfactory.</i>

Nausea: yes/no at 30 minutes and 1, 2, 3 and 24 hours postoperatively.

Vomiting: yes/no at 30 minutes and 1, 2, 3 and 24 hours postoperatively.

Pruritus: yes/no at 30 minutes and 1, 2, 3 and 24 hours postoperatively.

Dizziness: yes/no at 30 minutes and 1, 2, 3 and 24 hours postoperatively.

Headache: yes/no at 30 minutes and 1, 2, 3 and 24 hours postoperatively.

6.2.3 End of Treatment Visit

End of treatment is defined as 32 hours after first dose of study medicine taken as premedication, but the final visit in person is performed at 24 hours after first dose of study medicine as most patients leave the hospital the morning after surgery.

Data registered:

Blood pressure and heart rate are registered as part of ward routines.

Pain:

Pain at rest and while coughing, measured with NRS, is registered at 30 minutes, 1, 2, 3 and 24 hours postoperatively. Pain intensity difference (PID) at rest at 24 hours will be calculated from these values. Sum of pain intensity difference (SPID) at 24 hours is calculated as the time-weighted sum of the PID scores ($SPID\ t = \sum PID \times (time\ t - time\ t-1)$).

Pain relief, measured with categorical scale “none, slight, moderate, good or complete”, at 30 minutes, 1, 2, 3 and 24 hours postoperatively. Total pain relief (TOTPAR) over 24 hours will be calculated from these values.

Worst pain during 24 hours is measured with NRS.

Global medication performance (GMP) after 24 hours: “poor, fair, good, very good, excellent”.

Time to first rescue medicine (IV and/or PO) and total rescue analgesic consumption IV and PO over 24 hours is also registered.

Respiratory depression:

Oxygen saturation measured by pulse oximetry and respiratory rate measured at rest at 24 hours postoperatively.

Sedation:

Sedation is evaluated at 24 hours postoperatively using the Pasero opioid-induced sedation scale.

Table 1. Pasero Opioid-induced Sedation Scale (POSS) With Interventions*

S = Sleep, easy to arouse

Acceptable; no action necessary; may increase opioid dose if needed

1. Awake and alert

Acceptable; no action necessary; may increase opioid dose if needed

2. Slightly drowsy, easily aroused

Acceptable; no action necessary; may increase opioid dose if needed

3. Frequently drowsy, arousable, drifts off to sleep during conversation

Unacceptable; monitor respiratory status and sedation level closely until sedation level is stable at less than 3 and respiratory status is satisfactory; decrease opioid dose 25% to 50%¹ or notify prescriber² or anesthesiologist for orders; consider administering a non-sedating, opioid-sparing nonopioid, such as acetaminophen or an NSAID, if not contraindicated.

4. Somnolent, minimal or no response to verbal or physical stimulation

Unacceptable; stop opioid; consider administering naloxone^{3,4}; notify prescriber² or anesthesiologist; monitor respiratory status and sedation level closely until sedation level is stable at less than 3 and respiratory status is satisfactory.

Nausea: yes/no at 24 hours postoperatively.

Vomiting: yes/no at 24 hours postoperatively.

Pruritus: yes/no at 24 hours postoperatively.

Dizziness: yes/no at 24 hours postoperatively.

Headache: yes/no at 24 hours postoperatively.

To ensure patient safety the patient will be contacted at 32 hours, either in person or by phone if she is discharged from the hospital, with regards to adverse events (see paragraph 8.4).

End of trial will be at last point of contact made in person or by telephone at 32 hours.

6.2.4 Withdrawal Visit

The patient may withdraw from the study at any time without stating a cause for withdrawal.

6.2.5 After End of Treatment (Follow-up)

Not applicable.

6.3 Criteria for Patient Discontinuation

Patients may be discontinued from study treatment and assessments at any time. Specific reasons for discontinuing a patient for this study are:

- Voluntary discontinuation by the patient who is at any time free to discontinue her participation in the study, without prejudice to further treatment.
- Safety reason as judged by the Principal Investigator.
- Major protocol deviation (e.g. change of type of surgery after randomization; other analgesic or sedative medication administered; other factor as judged by Principal investigator).
- Incorrect enrolment i.e., the patient does not meet the required inclusion/exclusion criteria for the study.
- Deterioration in the patient's condition which in the opinion of the Principal Investigator warrants study medication discontinuation (to be recorded as an AE or under Investigator Discretion).
- Patient's non-compliance to study treatment and/or procedures.

6.4 Procedures for Discontinuation

6.4.1 Patient Discontinuation

Patients who withdraw or are withdrawn from the study will stop further treatment. Patients who withdraw or are withdrawn from study treatment will be followed up if any study medication has been administered in case of adverse events.

If possible, a final assessment shall be made (end of study visit). This to ensure that the patient receives information about reason for withdrawal and why she is not included in the study. The reason for discontinuation shall be recorded.

The investigator is obliged to follow up any significant adverse events until the outcome either is recovered or resolved, recovering/resolving, not recovered/not resolved, recovered/resolved with sequelae, fatal or unknown.

All patients randomized will be included in the study population.

Patients who withdraw or are withdrawn from the study after randomization may be replaced.

6.4.2 Trial Discontinuation

The whole trial may be discontinued at the discretion of the Principal investigator or the sponsor in the event of any of the following:

- Occurrence of AEs unknown to date in respect of their nature, severity and duration.
- Medical or ethical reasons affecting the continued performance of the trial.
- Difficulties in the recruitment of patients.

- Cancellation of drug development.
- Changes in funding to research team.

The sponsor and principal investigator(s) will inform all investigators, the relevant Competent Authorities and Ethics Committees of the termination of the trial along with the reasons for such action. If the study is terminated early on grounds of safety, the Competent Authorities and Ethics Committees will be informed within 15 days.

6.5 Laboratory Tests

Not applicable.

7 ASSESSMENTS

7.1 Assessment of Efficacy Response

The following parameters of response will be recorded:

Procedure for the primary efficacy parameter – Analgesic effect

Pain:

Baseline pain measured with NRS is done 15 minutes after extubation.

Pain at rest and while coughing, measured with NRS, is registered at 30 minutes, 1, 2, 3 and 24 hours postoperatively. Pain intensity difference (PID) at rest at 30 minutes, 1, 2, 3 and 24 hours will be calculated from these values. Sum of pain intensity difference (SPID) at 24 hours is calculated as the time-weighted sum of the PID scores ($SPID\ t = \sum PID \times (time\ t - time\ t-1)$).

Pain relief, measured with categorical scale “none, slight, moderate, good or complete”, at 30 minutes, 1, 2, 3 and 24 hours postoperatively. Total pain relief (TOTPAR) over 24 hours will be calculated from these values.

Worst pain during 24 hours is measured with NRS.

Global medication performance (GMP) after 24 hours: “poor, fair, good, very good, excellent”.

Time to first rescue medicine (IV and/or PO) and total rescue analgesic consumption IV and PO over 24 hours is also registered.

Procedure for the secondary efficacy parameters – Respiration

Respiratory depression: In the postoperative ward: continuous measurement of ETCO₂ with Smart CapnoLine® Plus (Microstream®), data are collected at 30, 60, 120, 180 minutes postoperatively. Respiratory rate at rest is measured at 30, 60, 120, 180 minutes postoperatively. Any episodes of ETCO₂ > 7.0 or respiratory rate < 10 are also recorded.

In the gynecological ward: oxygen saturation measured by pulse oximetry and respiratory rate measured at rest at 24 hours postoperatively.

Sedation: Sedation is associated with respiratory depression and evaluated at 30 minutes and 1, 2, 3 and 24 hours postoperatively, using the Pasero opioid-induced sedation scale.

Table 1. Pasero Opioid-induced Sedation Scale (POSS) With Interventions^a

S = Sleep, easy to arouse
<i>Acceptable; no action necessary; may increase opioid dose if needed</i>
1. Awake and alert
<i>Acceptable; no action necessary; may increase opioid dose if needed</i>
2. Slightly drowsy, easily aroused
<i>Acceptable; no action necessary; may increase opioid dose if needed</i>
3. Frequently drowsy, arousable, drifts off to sleep during conversation
<i>Unacceptable; monitor respiratory status and sedation level closely until sedation level is stable at less than 3 and respiratory status is satisfactory; decrease opioid dose 25% to 50%¹ or notify prescriber² or anesthesiologist for orders; consider administering a non-sedating, opioid-sparing nonopioid, such as acetaminophen or an NSAID, if not contraindicated.</i>
4. Somnolent, minimal or no response to verbal or physical stimulation
<i>Unacceptable; stop opioid; consider administering naloxone^{3,4}; notify prescriber² or anesthesiologist; monitor respiratory status and sedation level closely until sedation level is stable at less than 3 and respiratory status is satisfactory.</i>

7.2 Safety and Tolerability Assessments

Safety will be monitored by the assessments described below as well as the collection of AEs at every visit. Significant findings that are present prior to the signing of informed consent must be included in the relevant medical history/ current medical condition page of the CRF. For details on AE collection and reporting, refer to Section 8.

For the assessment schedule refer to Flow chart in Section 6.

Physical examination as part of standard preoperative examination by the gynecologist will include an examination of heart, lung, gynecological status, height and weight.

Vital signs include:

Preoperatively: blood pressure, pulse.

Perioperatively: Continuous 5-lead ECG, heart rate, BIS, ETCO₂ and SpO₂ measurement throughout the perioperative period. Minimum/maximum blood pressures are registered. Patients are monitored at all times during anesthesia by a nurse anesthetist.

Postoperatively: Continuous monitoring with 3-lead ECG, heart rate, ETCO₂, SpO₂ and intermittent monitoring of blood pressure and respiratory rate while in postoperative ward. Patients are monitored by nurses according to hospital standards during the stay in the postoperative ward. In the gynecological ward: SpO₂ and respiratory rate measured at rest at 24 hours postoperatively. Patients are monitored by nurses according to hospital standards during the stay in the gynecological ward.

Pain at rest and while coughing, measured with NRS, is registered at 30 minutes, 1, 2, 3 and 24 hours postoperatively.

Sedation is evaluated at 30 minutes and 1, 2, 3 and 24 hours postoperatively, using the Pasero opioid-induced sedation scale.

Other safety assessments are done according to standard procedure for in-hospital surgical patients.

7.3 Other Assessments

Assessment of predictive factors for postoperative pain will be done by questionnaire distributed to the patients 1-14 days before surgery.

Questionnaire

Preoperative pain:

Have you had pain related to the condition you are about to undergo surgery for during the last 7 days?

Yes/No.

If yes, how much of the time has the pain been present?

Sporadic/about half the time/more than half the time/continuously.

If yes, how painful is it on average?

NRS score 0 – 10.

Have you had pain not related to the condition you are about to undergo surgery for during the last 7 days?

Yes/No.

Is this pain diagnosed and/or related to a condition? If so, which condition?

If yes, how much of the time has the pain been present?

Sporadic/about half the time/more than half the time/continuously.

If yes, how painful is it on average?

NRS score 0 – 10.

Anxiety:

Have you been diagnosed with and/or treated for anxiety by a physician or another health care professional (i.e. psychologist, other)?

No/Yes, once/Yes, several occasions/Yes, on-going treatment.

Depression:

Have you been diagnosed with and/or treated for depression by a physician or another health care professional (i.e. psychologist, other)?

No/Yes, once/Yes, several occasions/Yes, on-going treatment.

Catastrophizing:

How would you best describe your attitude towards difficulties and problems in general:

I'm an optimist by nature/I'm neither an optimist nor a pessimist/ I tend to think about what can go wrong in a situation.

8 SAFETY MONITORING AND REPORTING

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an adverse event (AE) or serious adverse event (SAE). Each patient will be instructed to contact the investigator/study team immediately should they manifest any signs or symptoms they perceive as serious.

Personnel involved in the handling of the patient during the hospital stay will be informed about the study. The nurse anesthetists and nursing staff in the postoperative and the gynecological wards will receive information about the intervention and possible adverse effects. The expected adverse effects from the study drug should also be well known to nursing staff as they are the same as from standard treatment with opioids. The observation and description of side-effects/adverse events are part of standard nursing observations of the surgical patient receiving opioids.

The methods for collection of safety data are described below. The CRF will have a separate AE/SAE/SUSAR section for documentation. Any events after the end of study that the investigators are made aware of will be recorded as AE, SAE or SUSAR and reported to sponsor accordingly.

8.1 Definitions

8.1.1 Adverse Event (AE)

An AE is any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

The term AE is used to include both serious and non-serious AEs.

The following side-effects/adverse events: respiratory depression, sedation, nausea, vomiting, pruritus, dizziness and headache will be registered as part of end-points of interest. Further adverse events listed in the SmPCs for the study drugs will not be registered routinely.

If an abnormal vital sign is associated with clinical signs and symptoms, the sign/symptom should be reported as an AE and the associated vital sign should be considered additional information that must be collected on the relevant CRF.

8.1.2 Serious Adverse Event (SAE)

Any untoward medical occurrence that at any dose:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

Examples of possible SAE in our study:

- Respiratory depression which may be life-threatening and/or require prolonged hospitalization and/or result in persistent disability.
- Cardiovascular collapse secondary to respiratory depression or due to anaphylactic reactions or vasodilatation by other mechanisms.
- Anaphylactoid or anaphylactic reactions.

Prolonged hospitalization due to unmanaged pain at the end of the study is not recorded as SAE as this is a common reason for extended stay after surgery and according to hospital standards.

Medical and scientific judgment is to be exercised in deciding on the seriousness of a case. Important medical events may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent one of the listed outcomes in the definitions above. In such situations, or in doubtful cases, the case should be considered as serious. Hospitalization for administrative reason (for observation or social reasons) is allowed at the investigator's discretion and will not qualify as serious unless there is an associated adverse event warranting hospitalization.

8.1.3 Suspected Unexpected Serious Adverse Reaction (SUSAR)

Suspected Unexpected Serious Adverse Reaction: SAE (see section 8.1.2) that is unexpected as defined in section 8.2 and possibly related to the investigational medicinal product(s).

This protocol has included a range of symptoms and vital signs which are well-known side-effects/adverse events to all opioids, including the study medicines. Any such event mentioned in the protocol will be considered as SAE. Any event other than those mentioned in the SmPCs of the study medicines may be classified as SUSAR.

8.2 Expected Adverse Events

The following side-effects/adverse events: respiratory depression, sedation, nausea, vomiting, pruritus, dizziness and headache will be registered in the CRF as part of end-points of interest.

Examples of possible SAE in our study:

- Respiratory depression which may be life-threatening and/or require prolonged hospitalization and/or result in persistent disability.
- Cardiovascular collapse secondary to respiratory depression or due to anaphylactic reactions or vasodilatation by other mechanisms.
- Anaphylactoid or anaphylactic reactions.

Such AEs will be registered in the AE/SAE section of the CRF. Further adverse events listed in the SmPCs for the study drugs will also be registered as AE/SAE if they occur.

Investigational medicinal products SmPCs; section:

- 1) Palexia 50-100 mg, Grünenthal GmbH, Norwegian version section 4.8 "Bivirkninger".
- 2) Palexia depot 25-250 mg, Grünenthal GmbH, Norwegian version section 4.8 "Bivirkninger".
- 3) OxyNorm 5-20 mg, Mundipharma AS, Norwegian version section 4.8 "Bivirkninger".
- 4) OxyContin 5-120 mg, Mundipharma AS, Norwegian version 4.8 "Bivirkninger".

8.3 Disease Progression/Recurrence

Not applicable.

8.4 Time Period for Reporting AE and SAE

For each patient the standard time period for collecting and recording AE and SAEs will begin at start of study medicine and will continue until end of treatment as defined in paragraph 5.3. All patients will be screened for AEs/SAEs at 32 hours, contact will be made either in person or by phone if the patient is discharged from the hospital.

During the course of the study all AEs and SAEs will be proactively followed up for each patient; events should be followed up to resolution, unless the event is considered by the investigator to be unlikely to resolve due to the underlying disease. Every effort should be made to obtain a resolution for all events, even if the events continue after discontinuation/study completion.

8.5 Recording of Adverse Events

If the patient has experienced adverse event(s), the investigator will record the following information in the CRF:

- The nature of the event(s) will be described by the investigator in precise standard medical terminology (i.e. not necessarily the exact words used by the patient).
- The duration of the event will be described in terms of event onset date and event ended data.
- The intensity of the adverse event will be described by the investigator in precise standard medical terminology. The event will later be classified according to the International Conference on Harmonisation of Technical Requirements of Pharmaceutical for Human Use system MedDRA.
- The Causal relationship of the event to the study medication will be assessed as one of the following (15):

Table 2. WHO-UMC Causality Categories

Causality term	Assessment criteria*
Certain	<ul style="list-style-type: none">• Event or laboratory test abnormality, with plausible time relationship to drug intake• Cannot be explained by disease or other drugs• Response to withdrawal plausible (pharmacologically, pathologically)• Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon)• Rechallenge satisfactory, if necessary
Probable/ Likely	<ul style="list-style-type: none">• Event or laboratory test abnormality, with reasonable time relationship to drug intake• Unlikely to be attributed to disease or other drugs• Response to withdrawal clinically reasonable• Rechallenge not required
Possible	<ul style="list-style-type: none">• Event or laboratory test abnormality, with reasonable time relationship to drug intake• Could also be explained by disease or other drugs• Information on drug withdrawal may be lacking or unclear
Unlikely	<ul style="list-style-type: none">• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible)• Disease or other drugs provide plausible explanations
Conditional/ Unclassified	<ul style="list-style-type: none">• Event or laboratory test abnormality• More data for proper assessment needed, or• Additional data under examination
Unassessable/ Unclassifiable	<ul style="list-style-type: none">• Report suggesting an adverse reaction• Cannot be judged because information is insufficient or contradictory• Data cannot be supplemented or verified

*All points should be reasonably complied with

- Action taken.
- The outcome of the adverse event – whether the event is resolved or still ongoing.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 8.1. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but is not an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke, but would be an SAE.

8.6 Reporting Procedure

8.6.1 AEs and SAEs

All adverse events and serious adverse events that should be reported as defined in section 8.1.1 and 8.1.2 will be recorded in the patient's CRF.

SAEs must be reported by the investigator to sponsor within 24 hours after the site has gained knowledge of the SAE. Every SAE must be documented by the investigator on the SAE pages (to be found in the investigator site file). The Serious Adverse Event Report Form must be completed, signed and sent to sponsor (see page 2 for contact details). The initial report shall promptly be followed by detailed, written reports if necessary. The initial and follow-up reports shall identify the trial subjects by unique code numbers assigned to the latter.

The sponsor keeps detailed records of all SAEs reported by the investigators and performs an evaluation with respect to causality and expectedness. Based on, among other, SAE reports the sponsor will evaluate whether the risk/benefit ratio associated with study is changed.

The sponsor will further report the event/s to The Norwegian Medicinal Agency.

In case of a serious adverse event resulting in death the regional ethics committee (REK sør-øst C) should also be informed.

8.6.2 SUSARs

SUSARs will be reported to the Competent Authority (The Norwegian Medicines Agency and REK sør-øst C) according to national regulation. The following timelines should be followed:

The sponsor will ensure that all relevant information about suspected serious unexpected adverse reactions that are fatal or life-threatening is recorded and reported as soon as possible to the Competent Authority in any case no later than seven (7) days after knowledge by the sponsor of such a case, and that relevant follow-up information is subsequently communicated within an additional eight (8) days.

All other suspected serious unexpected adverse reactions will be reported to the Competent Authority concerned as soon as possible but within a maximum of fifteen (15) days of first knowledge by the sponsor.

SUSARs will be reported to The Norwegian Medicines Agency (post@legemiddelverket.no) using the CIOMS form no later than 7 days after the incident.

Sponsor will also report SUSAR to the EMEAs EudraVigilance database. This may be done with assistance from Grünenthal or Mundipharma.

8.6.3 Annual Safety Report

Once a year throughout the clinical trial, the sponsor will provide the Competent Authority (The Norwegian Medicines Agency) with an annual safety report. The format will comply with national requirements (i.e. "Årsrapport for ikke-kommersielle klinisk legemiddelutprøving").

8.6.4 Clinical Study Report

The adverse events and serious adverse events occurring during the study will be discussed in the safety evaluation part of the Clinical Study Report.

8.7 Procedures in Case of Emergency

The investigator is responsible for assuring that there are procedures and expertise available to cope with emergencies during the study.

- The randomization code will be stored in Harald Lenz's private office, Department of Anesthesiology, Oslo University Hospital, building 7, Ullevål. For safety reasons a sealed copy of the randomization code will also be available in the gynecological postoperative ward during the study. This will be accessible 24/7. In case of an unexpected medical incident the code will be broken to ensure proper treatment. Each pill box organizer will have a corresponding sealed envelope with the randomization code for that pill box organizer. This will enable us to identify the study medication given to one single patient without breaking the full randomization code.
- All medical staff involved in handling of patients should be trained in management of respiratory depression as part of professional training, but specific instructions in case of respiratory depression will be provided. These instructions will follow the patient at gynecological and postoperative ward (foiled version kept along with the pill box organizer and instructions):

Interventions if SpO₂ < 90% for more than 3 minutes or immediately if SpO₂ < 85% or respiratory rate < 10:

- 1) Stimulate patient to achieve respiratory rate > 10 and/or deeper respiratory action.
- 2) Supplemental oxygen increased to 5 l/min.
- 3) Reversal agent: Naloxon® (nalokson) 0.1 mg IV. Repeated every 2-5 minutes until response.
- 4) Bag-mask ventilation and consider other reasons for hypoxemia than opioid effect.

Other safety measures in case of unexpected incidents are according to standard procedures in the surgical, postoperative and gynecological wards.

9 DATA MANAGEMENT AND MONITORING

9.1 Case Report Forms

Case Report Forms (paper CRF/pCRF)

The CRF for this study will be designed and produced by research nurse Tomas Drægner and investigator Marlin Comelon, Oslo University Hospital, Ullevål.

The designated investigator staff will enter the data required by the protocol into the paper Case Report Forms (pCRF/CRF). The Investigator is responsible for assuring that data entered into the CRF is complete, accurate, and that

entry is performed in a timely manner. The signature of the investigator will attest the accuracy of the data on each CRF. If any assessments are omitted, the reason for such omissions will be noted on the pCRFs. Corrections, with the reason for the corrections will also be recorded.

The data will be entered into a database and double-checked for erroneous entries. The system used in this study is Filemaker Pro 14. The setup of the database system will be performed by research nurse Tomas Drægner, Oslo University Hospital, Ullevål.

After database lock, the investigator will receive a digital copy of the subject data for archiving at the investigational site.

9.2 Source Data

Source data are all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

For studies involving patients: The medical records for each patient should contain information which is important for the patient's safety and continued care, and to fulfill the requirement that critical study data should be verifiable.

To achieve this, the medical records of each patient should clearly describe at least ((CRF) = source data recorded directly into the Case Report Form; (HR) source data recorded in hospital records):

- That the patient is participating in the study, e.g. by including the enrollment number and the study code or other study identification (HR);
- Date when Informed Consent was obtained from the patient and statement that patient received a copy of the signed and dated Informed Consent (CRF);
- Results of all assessments confirming a patient's eligibility for the study (CRF);
- Diseases (past and current; both the disease studied and others, as relevant) (CRF, HR);
- Surgical history, as relevant (CRF, HR);
- Treatments given (CRF, HR);
- Visits to the clinic / telephone contacts during the study, including those for study purposes only (CRF, HR);
- Non-Serious Adverse Events and Serious Adverse Events (if any) including causality assessments (CRF, HR);
- Date of, and reason for, discontinuation from study treatment (CRF);
- Date of, and reason for, withdrawal from study (CRF);
- Date of death and cause of death, if available (HR);
- Additional information according to local regulations and practice (HR).

9.3 Study Monitoring

The investigator will be visited on a regular basis by the Clinical Study Monitor (Department of Clinical Research Support at Oslo University Hospital), who will check the following:

- Informed consent process

- Reporting of adverse events and all other safety data
- Adherence to protocol
- Maintenance of required regulatory documents
- Study Supply accountability
- Facilities and equipment (Storage of study medicine in the gynecological ward. Monitoring equipment such as Smart CapnoLine® Plus (Microstream®))
- Data completion on the CRFs including source data verification (SDV).

The monitor will review the relevant CRFs for accuracy and completeness and will ask the site staff to adjust any discrepancies as required.

Sponsor's representatives (e.g. monitors, auditors) and/or competent authorities will be allowed access to source data for source data verification in which case a review of those parts of the hospital records relevant to the study will be required.

9.4 Confidentiality

The investigator shall arrange for the secure retention of the patient identification and the code list. Patient files shall be kept for the maximum period of time permitted by each hospital. The study documentation (CRFs, Site File etc.) shall be retained and stored during the study and for 15 years after study closure. This will be kept in the research archive at the Department of Anesthesiology, Oslo University Hospital, Ullevål. All information concerning the study will be stored in a safe place inaccessible to unauthorized personnel.

The sponsor has the right to share de-identified individual-patient data (IPD) underlying the results presented in the final published article (including tables, figures, and appendices or supplementary material) should any journal or editor require this. The data underlying the results are defined as the IPD required to reproduce the article's findings, including necessary metadata. The confidentiality guidelines of Oslo University Hospital and REK sør-øst will be followed.

9.5 Database management

The data will be stored in a dedicated and secured area at:

- pCRF: in a locked filing cabinet in the office of investigator Marlin Comelon at the Department of Anesthesiology, Oslo University Hospital, building 7, Ullevål.

Data will be stored in a de-identified manner, where each study participant is recognisable by his/her unique trial subject number. The code list to link pCRF to patient in case of need for identifying data will be stored in a locked filing cabinet in the private office of research nurse Tomas Drægne at the Department of Anesthesiology, Oslo University Hospital, building 7, Ullevål.

After transferal of data from pCRF to the database (Filemaker Pro 14) the pCRF will be stored in in the research archive at the Department of Anesthesiology, Oslo University Hospital, building 36, Ullevål.

- The database will be stored in the designated space in the secure research server for Oslo University Hospital (Domain "Felles"-Sensitivt; File "Forskning03").

The data will be stored until 31.12.2035.

Data management will be performed by research nurse Tomas Drægne and investigator Marlin Comelon, Oslo University Hospital, Ullevål. The Data management procedures will be performed in accordance with the department's SOPs and ICH guidelines.

Data entered into the database will be validated by double-checking for erroneous entries against the CRF and hospital records.

Once the database has been completed and locked, the Sponsor will authorize database lock and all electronic data will be sent to the designated statistician for analysis. Subsequent changes to the database will then be made only by written agreement.

10 STATISTICAL METHODS AND DATA ANALYSIS

10.1 Determination of Sample Size

A previous study done by our research group on the treatment efficacy of oxycodone on acute pain after hysterectomy showed that patients had a mean numerical rating scale (NRS) score of 4 1 hour postoperatively, SD 1.5.(14) A non-inferiority margin of 10% of the total endpoint range (0-10) has been used previously, translating to an NRS score of 1.(7) If there is truly no difference between the treatments, then 72 completed patients are required to be 80% sure that the lower limit of a one-sided 97.5% confidence interval (or equivalently a 95% two-sided confidence interval) will exclude the non-inferiority margin of 1 in favor of the control treatment. To allow for 20% exclusions from the per-protocol population, we plan to randomize 90 patients.

10.2 Randomization

10.2.1 Allocation- sequence generation

- Method of generating the allocation sequence: computer-generated random sequential allocation. Harald Lenz will generate the allocation sequence.
- Allocation ratio: 1:1.
- Type of randomization: blocked randomization. Details of blocked randomization are provided in a separate document that is unavailable to those who enroll patients or assign treatment.

10.2.2 Allocation- procedure to randomize a patient

The study investigators will enroll the patients. After the informed consent form is collected, the patients will be allocated by choosing the next available treatment stored in sequentially numbered, opaque, sealed envelopes. The envelope will be opened a nurse or doctor not participating in the study. The study medication is dispensed in pill box organizers handed out by the ward nurse. This will ensure the blinding of the study investigators.

10.2.3 Blinding and emergency unblinding

The investigators and potentially the patient will be blinded for the randomization and the study medication. The patient may theoretically identify the study medication from drug characteristics, but we consider this unlikely. At the 24-hour visit we will ask the patient if she identified the medication or attempted to do so. However, to avoid any misunderstanding about patient blinding in a publication, we will describe the situation as is.

Harald Lenz and the colleague helping pack and label the study medicine will not be blinded, but will also not participate in the handling of the patients. The nurse breaking the envelopes for randomization will not be blinded, but he/she will not participate in the study otherwise.

Emergency unblinding should generally only be done if the safety and well-being of the patient is being compromised. The decision to reveal the treatment allocation during the study should be done exclusively by the principal investigator.

Un-blinding of the treatment allocation is permissible only if the safety and well-being of the patient is being compromised. The decision to reveal the treatment allocation during the study may only be done by the principal investigator. The date and time of un-blinding must be documented in the CRF and in the patient's hospital records.

In the event of an SAE, the Investigator may only break the treatment code if the appropriate future management of the patient necessitates knowledge of the current treatment. Although it is advantageous to retain the blind for all patients prior to final trial analysis, when an SAE may be a serious adverse reaction unexpected or otherwise judged reportable on an expedited basis, it is recommended that the blind should be broken only for that specific patient, by the sponsor or its designee, even if the Investigator has not broken the blinding.

10.3 Population for Analysis

The following populations will be considered for the analyses:

- The full analysis population: All randomized patients having received at least one dose of study medication and where a minimum of data is collected.
- The per-protocol population: All randomized patients completing the study without major protocol violations. Definition of major protocol violations will be specified in the statistical analysis plan, and the final criteria will be defined prior to database lock. Data concerning the primary endpoint should be collected.
- Safety population: Includes all randomized subjects who have received at least one dose of study medication. Subjects who withdraw from the study will be included in the safety analysis. A list of withdrawn subjects, preferably with the reasons for withdrawal, will be made.
- The primary statistical analysis will be based on the patients meeting the definition of the protocol population according to inclusion and exclusion criteria and with no major protocol violations. Since this is a non-inferiority study the per-protocol population is of major interest.
- The secondary analysis will include all patients receiving study treatment. Since this is a non-inferiority study the per-protocol population is of major interest.

10.4 Planned analyses

The main statistical analysis is planned when the planned number of patients have been included and have finalized data collection. Furthermore all data has to be entered, verified and validated according to the data management plan.

Prior to the main statistical analysis, the data base will be locked for further entering or altering of data. A separate statistical analysis plan (SAP) will provide further details on the planned statistical analyses. The SAP will be finalized, signed and dated prior to database lock. The treatment allocation will be revealed after the database lock and used in the statistical analysis. There will be no interim analysis.

Deviation from the original statistical plan will be described and justified in the Clinical Study Report. Amendments to plan can be done until day of DB lock.

10.5 Statistical Analysis

Statistical analysis will be done in SPSS (SPSS Inc., Chicago, IL). Parametric data will be analyzed with two-sided independent sample t-test or a linear mixed model where applicable. For non-parametric data the Mann Whitney U test will be used and for categorical data the Chi-squared test.

10.5.1 Primary analysis

The primary endpoint (pain score 1 hour postoperatively) will be assessed in the primary analysis set (the per-protocol population) using an independent two-sample t-distribution analysis.

Statistical hypothesis test:

- Null hypothesis: The difference in pain between the treatments is at least 1 point on the 0-10 NRS scale in favor of the control treatment.
- Alternative hypothesis: The difference in pain between the treatments is less than 1 point on the 0-10 NRS scale in favor of the control treatment.

The primary variable will be evaluated by the 95% confidence limits. A conclusion of non-inferiority will be made if the 95% confidence limits of the estimated treatment difference fully lie within the non-inferiority margin of 1 point on the 0-10 NRS scale. The non-inferiority margin was regarded as appropriate based on publications and discussions within the study committee. (7)

Mean values with 95% confidence limits will be used.

10.5.2 Secondary analyses

The following data will also be analyzed:

Between-group comparisons will be performed for the primary endpoint on secondary populations in addition to secondary efficacy endpoints on all populations.

Hypotheses testing

The between-group comparisons for secondary variables will be tested as for the primary variable where applicable and additional analyses will be performed based on the following methods (but not limited to):

- Continuous secondary variables will be subject to two-sample t-distribution analyses, repeated measures mixed models or appropriate non-parametric alternatives.
- Binary response variables will be analyzed using logistic regression (possibly adjusting for within-subject dependencies by generalized estimating equations) or chi-square/Mantel-Haenszel test.
- Time-to-event variables will be analyzed using the Kaplan-Meier method and comparisons between the two groups will be performed using the log rank test or Cox regression analyses.

Unless otherwise specified, all statistical hypotheses will be tested as the primary variable, i.e. with an assessment of non-inferiority based on the 95% confidence limits of the estimated difference between the groups. Non-inferiority margins of the secondary endpoints will be specified in the SAP prior to analysis. If the data indicate that one of the groups is superior to the other, a superiority test on the 5% significance level will be performed as for the primary variable on the ITT population. Thus, the non-inferiority analyses will be done in the PP population and the superiority analyses in the ITT population as appropriate.

Efficacy analyses

All patients included in the PP population will form the primary analysis population of the study. All efficacy analyses will be presented with estimates and 95% confidence limits of the treatment effect. For the primary variable specifically, this will be the estimated pain difference with corresponding 95% confidence limits.

Safety analyses

The safety analyses population will include all patients who completed the last point of contact at 32 hours postoperatively. Safety analyses will be descriptive and presented as summary tables by treatment group and (if applicable) by visit.

11 STUDY MANAGEMENT

11.1 Investigator Delegation Procedure

The principal investigator is responsible for making and updating a “delegation of tasks” listing all the involved co-workers and their role in the project. She will ensure that appropriate training relevant to the study is given to all staff, and that any new information of relevance to the performance of this study is forwarded to the staff involved.

11.2 Protocol Adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations.
All significant protocol deviations will be recorded and reported in the Clinical Study Report (CSR).

11.3 Study Amendments

If it is necessary for the study protocol to be amended, the amendment and/or a new version of the study protocol (Amended Protocol) must be notified to and approved by the Competent Authority and the Ethics Committee according to EU and national regulations.

11.4 Audit and Inspections

Authorized representatives of a Competent Authority and Ethics Committee may visit the center to perform inspections, including source data verification. Likewise, the representatives from sponsor may visit the center to perform an audit. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (ICH GCP), and any applicable regulatory requirements. The principal investigator will ensure that the inspectors and auditors will be provided with access to source data/documents.

12 ETHICAL AND REGULATORY REQUIREMENTS

The study will be conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice and applicable regulatory requirements. Registration of patient data will be carried out in accordance with national personal data laws.

12.1 Ethics Committee Approval

The study protocol, including the patient information and informed consent form to be used, must be approved by the regional ethics committee before enrolment of any patients into the study. The study was approved in the REK sør-øst C 31.05.17, reference number 2017/776/REK sør-øst C. The revised protocol sent to The Norwegian Medicines Agency 12.06.17 will also be submitted to REK sør-øst C.

The investigator is responsible for informing the ethics committee of any serious and unexpected adverse events and/or major amendments to the protocol as per national requirements.

12.2 Other Regulatory Approvals

The protocol will be submitted and approved by the applicable competent authorities before commencement of the study.

The protocol will also be registered in www.clinicaltrials.gov before inclusion of the first patient.

12.3 Informed Consent Procedure

The investigator is responsible for giving the patients full and adequate verbal and written information about the nature, purpose, possible risk and benefit of the study. They will be informed as to the strict confidentiality of their patient data, but that their medical records may be reviewed for trial purposes by authorized individuals other than their treating physician.

It will be emphasized that the participation is voluntary and that the patient can refuse further participation in the protocol whenever she/he wants. This will not prejudice the patient's subsequent care. Documented informed consent must be obtained for all patients included in the study before they are registered in the study. This will be done in accordance with the national and local regulatory requirements. The investigator is responsible for obtaining signed informed consent.

As the patients may be scheduled for surgery anytime between 1-14 days ahead the patients will primarily be contacted by mail with study information. This ensures information about the study a head of time and the patients are given ample time to reflect over their wish to participate. The patient will be contacted by phone the day before surgery to make time for questions and to let the investigators prepare for the inclusion the following day. If the patient is scheduled for surgery in only a few days' time, personal contact by telephone is made directly to inform about the study, but written study information will also be handed out on the day of surgery. The informed consent is collected by the study investigator on the day of surgery.

A copy of the patient information and consent will be given to the patients. The signed and dated patient consent forms will be filed in the Investigator Site File binder and also scanned to be part of the patient's electronic medical record at the hospital.

12.4 Subject Identification

The investigator is responsible for keeping a list of all patients (who have received study treatment or undergone any study specific procedure) including patient's date of birth and personal number, full names and last known addresses.

The patients will be identified in the CRFs by patient number, initials and date of birth.

13 TRIAL SPONSORSHIP AND FINANCING

The study is sponsored by funds from the Department of Anesthesiology, Oslo University Hospital.

14 TRIAL INSURANCE

For studies conducted in Norway: The Principal investigator has insurance coverage for the participants in this study through membership of the Drug Liability Association for the appropriate numbers included each year.

15 PUBLICATION POLICY

Upon study completion and finalization of the study report the results of this study will either be submitted for publication and/or posted in a publicly assessable database of clinical study results.

The results of this study will also be submitted to the Competent Authority and the Ethics Committee according to EU and national regulations.

All personnel who have contributed significantly with the planning and performance of the study (Vancouver convention 1988) may be included in the list of authors.

16 CONFLICT OF INTEREST

The investigators declare no conflicts of interest.

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18 LIST OF APPENDICES

- A Instructions on how to pack and label study medicine.
- B Labeling, information and log form for self-administration of study drug.
- C Questionnaire on predisposing factors for postoperative pain.

APPENDIX A

Instruksjoner for pakking og merking av studiemedisiner til Tapentadolstudien

Medikamentene skal pakkes og merkes av Harald Lenz med dobbeltkontroll fra sykepleier eller lege.

Det skal føres logg for pakking og merking som inneholder:

- Dosettnummer
- Batchnummere
- Dato for pakking og merking
- Signatur fra begge tilvirkere

Studiemedikamenter:

A: Palexia Depot (tapentadol depot) 50 mg tablett og Palexia (tapentadol) 50 mg tablett.

B: OxyContin (oxycodone extended-release) 10 mg tablett og OxyNorm 10 mg (oxycodone immediate-release) 10 mg kapsel.

Studiemedikamentene pakkes i identiske, nummererte dosetter. Dosettene plasseres i ugjennomsiktige, forseglede konvolutter med nummer som korresponderer med dosettene. I konvoluttene skal det også ligge et ark med instruksjoner for hvordan pasienten skal ta medisinene og der pasienten loggfører når medisinene tas. Instruksjonsarket skal ha nummerering i samsvar med dosetten. Dette arket inneholder også all påkrevet informasjon for merking av studiemedikamenter til bruk i klinisk studie (erstatte etikett). Dosettene vil allikevel ha en etikett som inneholder den viktigste informasjonen: «Til klinisk utprøving; Oppbevares utilgjengelig for barn; Se vedlagt bruksanvisning».

Pakking i dosett:

I dosettene skal det enten være Palexia Depot + Palexia ELLER OxyContin + OxyNorm.

Studiemedisin med langtidsvirkende effekt (enten Palexia Depot 50 mg eller OxyContin 10 mg) plasseres i lukene merket «Morgen» (1 tablett) og «Kveld» (1 tablett).

Studiemedisin med hurtigvirkende effekt (enten Palexia 50 mg eller OxyNorm 10 mg) plasseres i luken merket «Ved behov». I denne luken skal det ligge 4 tabletter/kapsler.

APPENDIX B

Instruksjoner og logging for Tapentadol-studien

Pasientens studienummer: _____

Pasientens initialer: _____

Dato for utlevering av medisin til pasient: _____

Bruksanvisning for medisindosett til klinisk utprøving av studiemedisin:

Luke Morgen:

Medisinen tas med maks et 1/2 glass vann 1 time før operasjon. Du vil få vite av sykepleier akkurat når du skal ta medisinen. Gi sykepleier beskjed om at du har tatt medisinen og noter tidspunktet du tok medisinen her:

kl _____

Luke Kveld:

Medisinen tas med ønsket mengde væske ca 12 timer etter første dose. Gi sykepleier beskjed om at du har tatt medisinen og noter tidspunktet du tok medisinen her:

kl _____

Luke Ved behov:

Her finner du 4 tabletter/kapsler med sterke smertestillende. Du kan ta **1** tablett/kapsel når du har økende smerter. Det må ha gått **minst 75 minutter (1 t og 15 min) mellom hver gang** du tar en tablett/kapsel. Gi sykepleier beskjed om at du tar medisinen og noter eventuelle tidspunkter du tok behovsmedisinen her:

kl _____

kl _____

kl _____

kl _____

Du kan ta total 4 tabletter/kapsler ved behov i løpet av de 24 timene studien pågår. Dersom dette ikke er tilstrekkelig eller det skulle oppstå andre behov tar du kontakt med sykepleieren din på sengeposten. Dersom du er godt smertelindret med medisinen du tar 1 time før operasjonen og 12 timer etter første dose, så trenger du ikke ta behovsmedisin.

Medisinene er kun til bruk i klinisk studie. Medisinene skal oppbevares i dosetten ved romtemperatur. Oppbevares utilgjengelig for barn. Ikke anvendte medikamenter returneres ved studiens avslutning.

Kontaktinformasjon til studiepersonell finner du på baksiden av dette arket.

Vedlegg i konvolutt nummer (= dosett id-nummer): _____

Sponsor: Avdelingsleder, Avdeling for anesthesiologi, Oslo Universitetssykehus, Ullevål.

Utpøringssted: Gynekologisk avdeling, Oslo Universitetssykehus, Ullevål.

Informasjon og merking av studiemedikamentet som er delt ut.

Protokollkode: EudraCT nummer 2017-001285-23.

Batch nummer: _____

Produksjonsdato: _____ **pakket av** _____ **(sign) /** _____ **(sign)**

Utløpsdato: _____

**Ansvarlig og forskrivende lege: Marlin Comelon, Avdeling for anesthesiologi, Oslo
Universitetssykehus, telefon 957 05 758.**

Studiemedisin inneholder enten Palexia 50 mg[®] (tapentadol 50 mg) og Palexia depot 50 mg[®] (tapentadol depot 50 mg) ELLER OxyNorm 10 mg[®] (oxycodone immediate-release 10 mg) og OxyContin 10 mg[®] (oxycodone extended-release 10 mg)

Utprøvere og kontaktpersoner for informasjon om legemiddelene, studien eller ved behov for avblinding (akutte medisinske tilfeller der man må avbryte studien og avsløre type medikament):

Marlin Comelon. Mobil: 957 05 758. Overlege ved anesthesiavdelingen, Ullevål.

Johan Ræder. Mobil: 922 49 669. Overlege ved anesthesiavdelingen, Ullevål.

Harald Lenz. Mobil: 905 49 545. Overlege ved anesthesiavdelingen, Ullevål.

Vedlegg i konvolutt nummer (= dosett id-nummer): _____

Sponsor: Avdelingsleder, Avdeling for anesthesiologi, Oslo Universitetssykehus, Ullevål.

Utprøvssteds: Gynekologisk avdeling, Oslo Universitetssykehus, Ullevål.

APPENDIX C

Questionnaire

Preoperative pain:

Have you had pain related to the condition you are about to undergo surgery for during the last 7 days?

Yes/No.

If yes, how much of the time has the pain been present?

Sporadic/about half the time/more than half the time/continuously.

If yes, how painful is it on average?

NRS score 0 – 10.

Have you had pain not related to the condition you are about to undergo surgery for during the last 7 days?

Yes/No.

Is this pain diagnosed and/or related to a condition? If so, which condition?

If yes, how much of the time has the pain been present?

Sporadic/about half the time/more than half the time/continuously.

If yes, how painful is it on average?

NRS score 0 – 10.

Anxiety:

Have you been diagnosed with and/or treated for anxiety by a physician or another health care professional (i.e. psychologist, other)?

No/Yes, once/Yes, several occasions/Yes, on-going treatment.

Depression:

Have you been diagnosed with and/or treated for depression by a physician or another health care professional (i.e. psychologist, other)?

No/Yes, once/Yes, several occasions/Yes, on-going treatment.

Catastrophizing:

How would you best describe your attitude towards difficulties and problems in general:

I'm an optimist by nature/I'm neither an optimist nor a pessimist/I tend to think about what can go wrong in a situation.

